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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/999,690	09/08/97	GUNZBURG W	GSF97-03A

HM12/0116

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EXAMINER	
LI,Q	
ART UNIT	**PAPER NUMBER**
1632	17

DATE MAILED: 01/16/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/999,690	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *30 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Nov. 30, 2000 has been entered.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Claim Rejections - 35 USC § 112

Claims 4-8, 10, 12-22, 25, 26, newly amended claims 1-3, 9, 11, 23, 24, and newly added claims 27-52, are rejected under 35 USC § 112, first paragraph for lack of adequate written description of the invention.

These claims recite "*therapeutic antimicrobial peptide or a biologically active derivative which is a part, analogue or homologue of the antimicrobial peptide*" The broadest reasonable meaning of these claims reads on a genus of antimicrobial peptides. Considering the exhibit B provided by the applicants, the examiner agrees to withdraw the rejection based upon "lytic peptides, not anti-microbial peptides or not anti-

tumor peptides". However, the rejection to a genus of antimicrobial peptides maintains because the specification fails to provide adequate written description as to the characteristic features how a structural changes may influence the biological activity of AMP derivatives. Adding a defining sentence "*which is a part, analogue or homologue of the antimicrobial peptide"* dose not overcome the rejection by the reasons given below.

As a genus, AMPs encompass a wide range of endogenously secreted peptides including lytic peptides and conventional antibiotics. Even within a species of lytic peptides, e.g. melittin and its analogues, one substitution or addition of amino acid residue may bring variation in its biological functions. It has been known in the art that melittin is a 26-residue peptide and certain residues may be associated with its membrane binding activity and other residues are essential for lytic activity (*Rivett et al.* Biochem J 1996; 316:525-29) at the time the priority of this application is claimed. Early studies have been focused on its secondary structural and functional relations in heomlytic activities (*Perez-Paya et al.*Biochem J 1994 Apr;299:587-91), catalytic activities (*Perez-Paya et al.* Pept Res 1994 7:286-8), and its surface properties (*Perez-Paya et al.* J Biochem 1995 270:1048-56). *Perez-Paya et al* teach "MINOR MODIFICATIONS IN THE AMINO ACID SEQUENCE OF MELITTIN RESULT IN DRAMATIC CHANGES IN ITS BIOLOGICAL ACTIVITY." (Biochem J 1994) "AMPHIPATHIC α-HELICES WERE FOUND TO BE A KEY DETERMINING FEATURE IN THE EARLY FOLDING PROCESS OF THE SELF ASSOCIATION OF PEPTIDES AND PROTEIN SEGMENTS. THOSE SUBSTITUTIONS, WHICH PREVENTED THE INDUCIBLE AMPHIPATHIC FOLDING ABILITY, WERE ALSO FOUND TO RESULT IN A LOSS IN HEMOLYTIC AND ANTIMICROBIAL ACTIVITY." (J Biochem 1995) According to above teachings, the antimicrobial activity of melittin analogues will vary significantly depending on the

position and components of amino acids residues. These variations can also be seen in Figures 9 and 10 of the instant specification. In these experiments with cecropin and melittin derivatives, tumor incidence is 69% in mice with control EJ cells, 100% in Cecropin-A10.8 and two groups of Pre Melittin-6 transduced tumor cells, 87% in Cecropin-A1.7 transduced tumor cells and 88% in Pre Pro Melittin-1 transduced cells, the results are apparently varied compared with the results from Ceropin A10.3 and A10.4 transduced cells. The specification fails to teach why these variation occurred and what kind of partial or combination of these derivatives will have antimicrobial activity.

Furthermore, bearing in mind the possible numbers of biologically active derivatives, the art known knowledge is "EACH POSITION IN A PEPTIDE IS UNIQUELY DEFINED, THE NUMBER OF POSSIBLE PEPTIDES IS VERY LARGE, EVEN IN A RELATIVELY SHORT PEPTIDE. WHEN THE NUMBER OF AMINO ACID UNITS IN THE PEPTIDE CHAIN EQUALS *N*, THE NUMBER OF POSSIBLE PEPTIDES IS 20^N. THE PREPARATION OF A SPECIFIC PEPTIDE SEQUENCE AND THE DETERMINATION OF THE SEQUENCE OF AMINO ACIDS IN A PEPTIDE OR PROTEIN CHAIN REQUIRES SPECIFICALLY ADAPTED CHEMICAL METHODS." (*Encyclopedia Britannica online*) The recited "AMP and their derivatives" in the claim surely encompass a large number of peptides, but their structural-functional relationship is not disclosed in the specification.

Considering the level of the skill and state of the art taught by *Boman, Perez-Paya, Rivitte et al*, the sequence and position of amino acid residue structure is extremely critical to the functions of AMPs. Without actual experimental evaluation, the results of making and using AMPs and their derivatives will be highly unpredictable in such a variable art (as shown by figures 9 and 10 of instant application). Therefore, the

information provided by the specification is not sufficient to enable one skill in the art recognize that the applicants had possession of the claimed invention as a whole at the time the application was filed and the priority is claimed.

Claims claims1-52, are rejected under 35 USC § 112, first paragraph for lack of enablement to its full scope.

These claims read on a genus of antimicrobial peptides including parts, analogue or homologue and combinations thereof. However, the specification fails to provide sufficient guidance regarding how to make a partial or combination, an analogue or homologue of AMPs so that these derivatives will be indeed capable of killing microorganisms. Adding a defining sentence "*which is a part, analogue or homologue of the antimicrobial peptide*" dose not overcome the rejection by the reasons given below.

The recited "AMP and their derivatives" in the claim surely encompass a large number of peptides, but their structural functional relationship is not disclosed in the specification. As explained in the written description rejection of this office action, AMPs are a largely variable art, without detailed disclosure about the structural-functional relations, the results of making these derivatives will be highly unpredictable.

In addition, applicants are reminded that not all tumors have a viral related pathogenesis and the art known knowledge is that AMPs are powerful in killing bacterial organism and fungi, only some of them such as defensin shown some antiviral activity (*Boman*, pg 79, 2nd paragraph) at the time the application claimed priority,

Claims 8, 34 recite "cell cycle regulatory peptides, tumor suppressor peptides, antiproliferation peptides and cytokines" which is not supported by the specification.

Considering the level of the skill and state of the art taught by *Boman, Perez-Paya, Rivitte et al*, and evidenced by figures 9, 10 of the instant specification, the sequence and position of amino acid residue structure is extremely critical to the functions of AMPs. Without actual experimental evaluation, the results of making and using AMPs and their derivatives will be highly unpredictable in such a variable art. The specification is not sufficient to enable one skill in the art making and using the invention to its full scope without undue experimentation.

Claims 1-52 are rejected under 35 USC § 112, first paragraph for lack of enablement of the claimed invention.

These claims recite "therapeutic antimicrobial peptide" "therapeutically effective amount" "a pharmaceutical composition" "method for introducing nucleotide sequences into a mammal" "a method for treating an individual having... disease" "a method for the treatment of a disease"

The nature of these claims reads on a gene therapy method *in vivo* in a mammal. However, the specification fails to provide any guidance as to whether the *in vivo* use of AMPs, their analogues, homologues and combinations thereof, will provide such antitumor and antiviral effect with a reasonable success and an acceptable level of side effects. Deleting the phrase "*for introducing DNA into an eukaryotic cell, the vector*" could not overcome the aspect of enablement rejection for a therapeutic method *in vivo*.

The examiner has considered but not accepted Exhibit A and B for the following reasons.

The *in vivo* working example in the specification is a pure experimental approach investigating the expression of AMPs and their derivatives to the growth of the transduced tumor cells. The model itself does not provide a method of treating a disease in a mammal with a *naturally occurred* "genetic defect, cancer and viral infections".

The only *in vivo* model system used in the "antitumor experiments" is an immune compromised mice injected with tumor cell line, which transduced with melittin or cecropin and derivatives thereof. The specification recites that these transduced cell-clones show "a reduced rate of tumor growth". However, the incidence of tumor after these cell-line injections shows large variations in figures 9 and 10. Tumor incidence is about 69% in mice with control EJ cells, 100% in Cecropin-A10.8 and two groups of Pre Melittin-6 transduced tumor cells, 87% in Cecropin-A1.7 transduced tumor cells and 88% in Pre Pro Melittin-1 transduced cells, these results are contrary to what is claimed.

Furthermore, the means and ways to treat a naturally occurred genetic defect, a tumor or a viral infection, which is essential to the claimed invention, are not disclosed in the specification.

Another important factor needs be considered for therapeutic use is the side effects of these AMPs and derivatives. All AMPs and their derivatives, which have an antimicrobial and antitumor activity, will also have a cytotoxic effect to the host. "THEY AVOID THE PROBLEM OF SELF-DESTRUCTION EITHER BY A CELLULAR COMPARTMENTALIZATION OR BY SPECIFICITY

FOR A MICROBIAL TARGET THAT IS ABSENT IN THE ANIMAL HOST" (Boman, pg. 62, 2nd paragraph). When given by a systemic method to a mammal host, the effect to normal cells of the host has to be evaluated. This aspect of claimed invention has not been disclosed by the applicants, therefore, the method is not enabled to use *in vivo* therapeutically.

Considering the nature of above claims, the variations of possible results, the guidance given in the specification, the level of skill and state of art at the time the application was filed and the priority is claimed, one skill in the art can not practice the claimed invention without undue experimentation.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly amended claims 1, 9, 23 exclude "defensin". However, the reason to such exclusion has not disclosed in the specification. Therefore, these amended claims introduced new matter to the claims.

Pending patent applications in the Supplemental IDS have been considered as requested by applicants. However, they are not persuasive to the issues of current rejection, such as lack of written description to the claimed peptides, and *in vivo* therapeutic use etc.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 410-308-7942. The examiner can normally be reached on 8:30 am - 5 pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are 410-308-4242 for regular communications and 410-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Deborah Clark

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QJL
January 2, 2001